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(54) Title: HYDROPHOBIC CARBOMER COMPLEX COMPOSITIONS

(57) Abstract

Hydrophilic carbomer complexes, such as bismuth or nicotine carbomer, are rendered hydrophobic at neutral to acid pH by milling to pass a 150 μm sieve screen and then impregnating with a water-insoluble anionic polymer. Preferred anionic polymers are partly methyl esterified methacrylic acid polymers.

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HYDROPHOBIC CARBOMER COMPLEX COMPOSITIONS

This invention relates to a hydrophobic powder of a complex, particularly bismuth carbomer and nicotine carbomer, pharmaceutical dosage forms, particularly enteric coated capsules containing said powder, its use in treating inflammatory bowel disease, and a method of preparing said hydrophobic powder.

Carboxypolymethylene polymers ("carbomers") are widely used in the pharmaceutical industry as dispersing, emulsifying, suspending or thickening agents. Usually, they are high molecular weight polymers of acrylic acid cross-linked with allylsucrose or allyl ethers of pentaerithritol. A range of carbomers is available from B. F. Goodrich under the Trade Mark CARBOPOL.

The presence of pendent carboxy groups in carbomers makes them ionic and permits of the formation of salts such as metal salts, and other complexes. Some of these complexes have pharmacological properties. For example, EP-A-0 293 885 discloses a complex of carbomer and erythromycin which has the advantages of masking the bitter taste of the erythromycin and improving its systemic absorption. To further reduce dissolution of the erythromycin in the mouth and thereby further mask the taste, the drug complex can be polymer coated with the most preferred being hydroxypropylmethycellulose phthalate.

Bismuth carbomer is useful for treating gastrointestinal disorders (see WO-A-9201457) and it has recently been found that nicotine carbomer is useful for treating inflammatory bowel disease (PCT/GB97/00369 - unpublished).

In Example 7 of WO-A-9201457, granules in the range of 0.5 - 2.1 mm were spray coated with Eudragit L, and then packed into hard gelatin capsules. In theory, the bismuth-carbomer complex should coat the walls of the intestine such that the mucoadhesive carbomer holds the bismuth insitu adjacent the mucosal wall to combat the inflammatory bowel disease. However, on investigation of the capsules of WO-A-9201457, the performance was less than expected.

The inventors, however, surprisingly discovered that an excellent dosage form of bismuth carbomer with much improved therapeutic potential could be formed by coating sub 150 μm particles of the carbomer complex with a water-insoluble anionic polymer.

More particularly the inventors discovered that the content of the capsules of WO-A-9201457 formed upon release a bolus or lumps in the intestine leading to sub-optimal covering of the mucosal wall. The present invention on the other hand supplies an elegant dispersion in the aqueous medium of the intestine and gives an excellent covering on the mucosal wall, thereby vastly improving the therapeutic effect of the bismuth carbomer complex. Early investigations have now shown that the invention can be applied to other hydrophilic carbomer complexes, more particularly to a nicotine carbomer complex.

Accordingly, it is an object of the present invention to provide a readily water-dispersible form of a hydrophilic carbomer complex and, in particular, a form which, on release in the gastrointestinal tract, will readily disperse without bolus-formation.

According to a first aspect, the present invention provides a hydrophobic powder comprising particles of a

hydrophilic carbomer complex passing a 150 μm sieve screen coated with a water-insoluble anionic polymer.

The method of forming the hydrophobic powder provides a further aspect of the invention. Conventionally it is very difficult to sufficiently coat such small particles, and the inventors found that typical hydrophobising substances such as polyglycolyzed wax, sorbitan monostearate and cetylpyridinium chloride also formed lumps when applied to hydrophilic carbomer complexes. Surprisingly when a water-insoluble anionic polymer was used on sub 150 μm particles, a sufficient coating was developed which caused the particles to disperse and swell as aforesaid.

Accordingly in a second aspect, the present invention provides a method of forming a readily water-dispersible composition of a hydrophilic carbomer complex which comprises coating particles of said complex passing a 150 μm sieve screen with a solution of a water-insoluble anionic polymer and drying the coated particles.

In a third aspect, the present invention provides a pharmaceutical composition comprising a pharmacologically-acceptable hydrophobic powder of the invention.

The coating on the particles can be a partial or complete coating or the particles can be impregnated with the anionic polymer, such that the coated particle first disperses before it swells and coats the mucosa.

It is preferred that 100% of the hydrophilic carbomer particles pass a 100 μm sieve screen (i.e. they are sub 100 μm), more preferably at least 90%, especially at least 95%, of the hydrophilic carbomer particles pass a 63 μm sieve screen, more preferably a 50 μm sieve screen. The precise

particle size must be small enough to provide a composition with a suitable degree of hydrophobicity following coating with the anionic polymer. Preferred particle size may vary according to the nature and amount of the cation present in the complex and the nature and amount of the anionic polymer.

The presently preferred anionic polymers are anionic carboxylic polymers, i.e. polymers in which the anionic groups are at least predominantly free carboxylic and/or esterified carboxylic groups. It is particularly preferred that the anionic polymer is an acrylic polymer and the presently most preferred polymers are partly methyl esterified methacrylic acid polymers such as poly(methacrylic acid, methyl methacrylate) in which the ratio of free acid groups to ester groups is about 1:1 ((e.g. those availably from Röhm Pharma GmbH under the Trade Mark EUDRAGIT L), or especially, about 1:2 ((e.g. those availably from Röhm Pharma GmbH under the Trade Mark EUDRAGIT S). In this connection, selection of a particular anionic polymer and the amount thereof can provide the hydrophilic particles with a desired dissolution profile.

The amount of anionic polymer used will depend upon the nature and amount of the cation present in the salt, the nature of the impregnating anionic polymer, and the degree of hydrophobicity required. A suitable amount can be determined by simple experimentation but usually the anionic polymer will be present in an amount of 10 to 50%, preferably 20 to 40, more preferably 25 to 35 and especially about one third, based on the weight of the carbomer complex. Having regard to the small particle size the amount of polymer will be less than the theoretical amount required to coat the particles, and the swelling and dissolution of the carbomer will not be controlled by pH.

For the avoidance of doubt the above % w/w also apply to the polymer used in the method of coating the particles.

Preferably an amount of water is present in the solvent/polymer mixture into which the carbomer particles are mixed.

Usually, the powder of the invention will be administered orally by loading into capsules, which usually will be coated to release the contents at the desired location in the gastrointestinal tract. Conveniently, the capsules will be a soft or, preferably, hard gelatin capsule although other capsules which will dissolve in the required part of the gastrointestinal tract can be used.

When it is desired to administer the carbomer complex to the small intestine, the capsule can be coated with an enteric coating which will protect it during passage through the stomach. Any conventional enteric coating material which is soluble in the small intestine can be used but the coating should release its contents at a pH below the threshold value at which the impregnated powder ceases to be hydrophobic and readily dispersible. Suitable coating materials include cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate or initially ethyl cellulose followed by polyvinyl acetate phthalate, but it is preferred to use an anionic polymer having an appropriate dissolution profile. The presently preferred polymers are anionic carboxylic polymers. It is particularly preferred that the polymers should be acrylic polymers and the presently most preferred polymers are partly methyl esterified methacrylic acid polymers in which the ratio of free acid groups to ester groups is about 1:1 (e.g. Eudragit™ L).

Preferably the carbomer complex are active in the treatment or maintenance of inflammatory bowel disease. Bismuth carbomer and nicotine carbomer are particularly preferred in accordance with the invention, especially for the treatment of inflammatory bowel disease.

It will be appreciated from the foregoing that reference to carbomer complex herein includes salts such as metal salts of carbomer.

Capsules containing bismuth or nicotine or other carbomer complexes required to be administered to the large intestine, preferably are coated with a coating which selectively dissolves in the large intestine or a specific area thereof. For example when treating colonic disorders such as ulcerative colitis or Crohn's colitis, it is preferred that the capsule coating is insoluble in gastric juice and in intestinal juice below pH 7 but is soluble in colonic intestinal juice whereby the coating remains substantially intact until the capsule reaches at least the ileum and, preferably, thereafter provides a sustained release of the drug in the colon. Suitably for this purpose, the coating comprises a partly methyl esterified methacrylic acid polymers in which the ratio of free acid groups to ester groups is about 1:2 (e.g. EUDRAGIT™ S).

The capsule coating can, and usually will contain plasticiser and possibly other coating additives such as colouring agents, gloss producers, talc and/or magnesium stearate as well known in the coating art. In particular, anionic carboxylic acrylic polymers usually contain 10 to 50, especially 10 to 25, percent by weight of a plasticiser especially triethylcitrate or diethyl phthalate.

Further, when an anionic polymers is used as the capsule coating, it can be used in admixture with neutral

water-insoluble but permeable polymers. The neutral insoluble but permeable polymers preferably are acrylic ester polymers, especially methylmethacrylate ester copolymers with ethylacrylate. Suitably, the molecular ratio of anionic polymer to neutral polymer, if present, is in the range 5:1 to 1:5, especially 3:1 to 1:3, most preferably 1:1 to 1:3.

Conventional coating techniques such as spray or pan coating are employed to apply the enteric coating to the capsules (See for example D. Dreher "Film coatings on acrylic resin basis for dosage forms with controlled drug release" Pharma International 1/2 (1975) 3.)

Further aspects of the invention are as follows:-

(a) use of hydrophobic powder according to the first aspect of the invention in the preparation of a medicament for the treatment of inflammatory bowel disease, particularly Crohn' disease and/or ulcerative colitis;

(b) a method for the treatment of inflammatory bowel disease comprising administering to the area of inflammation in the gastro-intestinal tract, a hydrophobic powder according to the first aspect of the invention;

(c) the use of an anionic polymer to render hydrophobic powder comprising particles of a hydrophilic carbomer complex passing a 150 μm sieve screen by impregnation thereof.

Preferred embodiments of the invention are as follows:-

(a) an enteric coated capsule containing a hydrophobic powder comprising particles of bismuth carbomer or nicotine carbomer complex having a particle size which pass a 150 μm sieve screen which are coated with a partly methyl esterified methacrylic acid polymer at from 20 to 40% by weight of the carbomer complex;

(b) a method of forming a readily water-dispersible composition of bismuth carbomer or nicotine carbomer complex comprising milling the carbomer complex and passing through a 150 μm sieve screen, adding the sieved particles to a mixture of solvent and partly methyl esterified methacrylic acid polymer at from 20 to 40% by weight of said carbomer particles, stirring, then evaporating the solvent to leave coated carbomer complex particles.

More preferably still, an alkylcitrate (such as triethylcitrate), a C_{1-4} alcohol (such as isopropanol), and water are present with the polymer in the solvent/polymer mixture. Advantageously, the bismuth particles are stirred into this mixture and the solvent then evaporated off under vacuum at between 40 to 80°C, most preferably between 50 - 70°C.

The following non-limiting Examples are provided to illustrate the invention:-

EXAMPLE 1

Bismuth carbomer (conventionally prepared from bismuth citrate and Carbopol™ 974 P) containing about 15% w/w bismuth was milled (micronized) until 95% of the particles

pass through a 50 µm sieve screen (99.9% < 98 µm, 80% < 10 µm).

Eudragit S 100 (39.33 g) and triethylcitrate (3.93 g) were slowly added to a stirred mixture of isopropanol (786.34 g) and water (39.33 g) and the mixture stirred until a clear solution was obtained. Micronized bismuth carbomer (131.07 g) was slowly added whilst stirring continued. The mixture was then stirred at 50 °C under -0.8 bar vacuum and the resultant vapour condensed. When the residue became powdery, the temperature was slowly raised to 70°C until no further vapour was produced. The resultant powder was cooled to 20 °C and the vacuum released. Any lumps in the product were crushed and the powder kept under vacuum at 70 °C for 4 hours to dry.

The resultant hydrophobic impregnated powder contained about 30% EUDRAGIT™ S and 5 to 10% moisture, thereby lowering the bismuth content of the powder to about 9.7 %w/w.

EXAMPLE 2

Nicotine carbomer (conventionally prepared from nicotine and Carbopol™ 974 P) containing about 2% w/w nicotine was milled (micronized) until 95% of the particles pass through a 50 µm sieve screen.

Eudragit S 100 (39.33 g) and triethylcitrate (3.93 g) were slowly added to a stirred mixture of isopropanol (786.34 g) and water (39.33 g) and the mixture stirred until a clear solution was obtained. Micronized nicotine carbomer (131.07 g) was slowly added whilst stirring continued. The mixture was then stirred at 50 °C under

-0.8 bar vacuum and the resultant vapour condensed. When the residue became powdery, the temperature was slowly raised to 70°C until no further vapour was produced. The resultant powder was cooled to 20 °C and the vacuum released. Any lumps in the product were crushed and the powder kept under vacuum at 70 °C for 4 hours to dry.

A hydrophobic impregnated nicotine carbomer powder was produced.

EXAMPLE 3

Hard gelatin size 0 capsules (2,000) were each filled with 436.6 mg of the impregnated bismuth carbomer powder of Example 1 and 4.4 mg magnesium stearate (lubricant) and spray coated (50 mg/capsule) with an aqueous dispersion of EUDRAGIT™ L containing:

Eudragit L 30 D-55	263.0 g
Triethylcitrate	27.6 g
Polysorbate 80 MO 55 F	0.6 g
Monostearin	1.5 g
Talc	1.4 g
Water	130.0 g

The aqueous dispersion was prepared as follows:

A first component was formed by stirring together triethylcitrate, Polysorbate 80 MO 55 F and Eudragit L 30 D-55.

A second component was prepared by heating some of the water (100 g) to 65 °C, adding monostearin and homogenizing to form an emulsion, which is cooled (15 mins) to room temperature whilst slowly stirring.

A third component was prepared by dispersing the talc in the remainder of the water (30 g).

The first component was filtered through a 105 μm filter; the filtrate stirred whilst slowly adding the second component via the same filter; and then the third component added while continuing stirring.

The coated capsule was resistant to 0.1N hydrochloric acid solution for 2 hours but rapidly disintegrated at pH 5.5 or above. The dispersion of the powder following disintegration of the capsules was tested by two different methods. In the first method, each test capsule was placed on the surface of 100 cm^3 phosphate-buffer solution (pH 5.5, 6.0 or 6.5) at 37°C in a 250 cm^3 beaker stirred at 60 rpm by a magnetic stirrer. The times taken for capsule disintegration and content dispersion were observed. In the second method, each test capsule was subjected to the disintegration test described in US Pharmacopoeia XXII using a phosphate buffer solution (pH 5.5, 6.0 or 6.5) at 37°C.

The same disintegration and dispersion times were observed for both test and these are set forth in Table 1 below:

TABLE 1

Media pH	Capsule Disintegration (mins)	Complete Powder Dispersion (mins)
5.5	45	45
6.0	40	35
6.5	10	30

In contrast with the above data, when the powder was not impregnated (but in an identical capsule) lumps of bismuth carbomer were formed and only partly dispersed.

When the tests were repeated at pH greater than 6.8, the impregnated powder was not completely dispersed. Accordingly, for satisfactory administration of capsules containing the impregnated capsules of Example 1, the capsule coating should dissolve between pH 5.5 and 6.5.

Aqueous 1M sodium hydroxide was slowly added to a gently stirred pH 6.5 phosphate buffer solution containing completely dispersed bismuth carbomer powder (following the disintegration therein of a capsule of Example 1) to raise the pH thereof and cause the powder to dissolve. The viscosity of the solution rises as the concentration of bismuth carbomer and the pH increase as set forth in Table II below.

TABLE II

Capsules No/100 cm^3	Bismuth Carbomer g/100 cm^3	Viscosity cps (mPa.s) pH 6.4	pH 7.0	pH 7.5
3^1	0.825	12	27	27
4^2	1.100	56	882	1,040
5^2	1.375	481	1,600	2,000
6^2	1.650	1,200	4,410	4,980
8^2	2.200	4,490	7,480	11,400
10^2	2.750	20,000	40,100	39,800

[1] Brookfield DVII spindle 62; 60 rpm

[2] Brookfield DVII spindle 63; 1.5 rpm

After reaching pH 7.5, the solutions were allowed to stand for 48 hours and then their viscosities remeasured. The results are set forth in following Table III:

TABLE III

Capsules No/100 cm^3	Viscosity cps (mPa.s) at pH 7.5
3^2	638
4^2	4,490
5^2	16,300
6^2	26,100
8^3	337,000
10^3	>400,000

[2] Brookfield DVII spindle 63; 1.5 rpm

[3] Brookfield DVII spindle 63; 0.3 rpm

It will be appreciated that the invention is not restricted to the particular details disclosed and that numerous modifications and variations can be made without departing from the scope of the invention as defined in the following claims.

CLAIMS:

1. A hydrophobic powder comprising particles of a hydrophilic carbomer complex passing a 150 μm sieve screen coated with a water-insoluble anionic polymer.

2. A hydrophobic powder as claimed in Claim 1 wherein the particles of hydrophilic carbomer particles pass a 100 μm sieve screen.

3. A powder as claimed in Claim 2 wherein at least 90% of the hydrophilic carbomer particles pass a 50 μm sieve screen.

4. A powder as claimed in any one of Claims 1 to 3, wherein the anionic polymer is an anionic carboxylic polymer.

5. A powder as claimed in Claim 4, wherein anionic polymer is a partly methyl esterified methacrylic acid polymer.

6. A powder as claimed in Claim 5, wherein the acrylic polymer is a partly methyl esterified methacrylic acid polymer in which the ratio of free acid groups to ester groups is about 1:1.

7. A powder as claimed in Claim 5, wherein the acrylic polymer is a partly methyl esterified methacrylic acid polymers in which the ratio of free acid groups to ester groups is about 1:2.

8. A powder as claimed in any one of the preceding claims, wherein the anionic polymer content is from 20 to 40% based on the weight of the carbomer complex.

9. A powder as claimed in Claim 8, wherein the amount of anionic polymer is about one third based on the weight of the carbomer complex.

10. A powder as claimed in any one of the preceding claims, wherein the carbomer complex is bismuth carbomer.

11. A powder as claimed in any one of Claims 1 to 9, wherein the carbomer complex is nicotine carbomer.

12. A pharmaceutical composition comprising a pharmacologically-acceptable hydrophobic powder as claimed in any one of Claims 1 to 11.

13. A composition as claimed in Claim 12, wherein the powder is contained within a capsule.

14. A composition as claimed in Claim 13, wherein the capsule is enteric coated to release the contents at a desired location in the gastrointestinal tract.

15. A composition as claimed in Claim 14, wherein the capsule is coated with an anionic carboxylic polymer-containing coating.

16. A composition as claimed in Claim 15, wherein the anionic polymer of the capsule coating is a partly methyl esterified methacrylic acid polymer.

17. A composition as claimed in Claim 16, wherein the anionic polymer of the capsule coating is a partly methyl esterified methacrylic acid polymer in which the ratio of free acid groups to ester groups is about 1:1

18. A composition as claimed in Claim 16, wherein the anionic polymer of the capsule coating is a partly methyl

esterified methacrylic acid polymer in which the ratio of free acid groups to ester groups is about 1:2

19. An enteric coated capsule containing a hydrophobic powder comprising particles of bismuth carbomer or nicotine carbomer complex having a particle size which pass a 150 μm sieve screen which are coated with a partly methyl esterified methacrylic acid polymer at from 20 to 40% by weight of the carbomer complex.

20. Use of a powder as defined in any one of Claims 1 to 11 in the preparation of a medicament for the treatment of inflammatory bowel disease.

21. The use of an anionic polymer to render hydrophilic a powder comprising particles of a hydrophilic carbomer complex passing a 150 μm sieve screen by impregnation thereof.

22. A use as claimed in Claim 21, wherein the carbomer salt of the polymer is as defined in any one of Claims 2 to 11.

23. A method of forming a readily water-dispersible composition of a hydrophilic carbomer complex which comprises coating particles of said complex passing a 150 μm sieve screen with a solution of a water-insoluble anionic polymer and drying the coated particles.

24. A method as claimed in Claim 23, wherein the carbomer salt of the polymer is as defined in any one of Claims 2 to 11.

25. A method as claimed in Claims 23 or 24 wherein the carbomer complex is added to a mixture of the anionic

polymer and solvent, and the solvent evaporated to leave the coated carbomer particles.

26. A method as claimed in Claim 25 wherein the anionic polymer is used in an amount of 20 to 40% by weight of the carbomer complex.

27. A method of forming a readily water-dispersible composition of bismuth carbomer or nicotine carbomer complex comprising milling the carbomer complex and passing through a 150 µm sieve screen, adding the sieved particles to a mixture of solvent and partly methyl esterified methacrylic acid polymer at from 20 to 40% by weight of said carbomer particles, stirring, the evaporating the solvent to leave coated carbomer complex particles.

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INTERNATIONAL SEARCH REPORT

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PCT/EP 97/01847

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/14 A61K9/50 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 514 008 A (TAKEDA CHEMICAL INDUSTRIES) 19 November 1992 see page 3, line 35-56; claims 1-4,17 see page 5, paragraph 2; claims 23,28,32 see page 7, paragraph 1-5; claim 34 see page 9, paragraph 2-5 see page 10, paragraph 3; table 2 --- -/--	1,4-7, 12,13, 20-25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 October 1997	14/11/1997

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk	

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 92 01457 A (RHODES JOHN) 6 February 1992 cited in the application see page 2, line 8-10; example 7 see page 4, line 17-32; claims 1-3,7-10 see page 5, line 25-29; claims 12,16,20,21 see page 8, line 17 - page 10, line 6 see page 10, line 25-28 see page 11, line 6-18; claims 24,28 see page 11, line 28 - page 12, line 4 see page 12, line 22-25	1,4-10, 12-27
A	EP 0 293 885 A (ABBOTT LAB) 7 December 1988 cited in the application see page 3, line 57 - page 4, column 27 see page 5, line 16-40; claims 6,7,9-11,13; example 5	1,4-7, 12,13, 23-25
X	EP 0 526 862 A (VECTORPHARMA INTERNATIONAL SPA) 10 February 1993	1,4-7, 10,12, 13,19,20
A	see page 4, line 46-47; claims 1,3 see page 4, line 50-51; example 6C see page 5, line 9-24 see page 5, line 50-56 see page 7, column 2-3 see page 7, line 39-46 see page 7, line 56-57	23-27
A	EP 0 587 106 A (VECTORPHARMA INTERNATIONAL SPA) 16 March 1994 see page 3, line 28-34; claims 12,14,15 see page 3, line 53-56; claims 21-24	1,4-7,12
A	DE 22 46 037 A (TAESCHNER & CO) 11 April 1974 see page 3, paragraph 4 - page 4, paragraph 1; claims 1,2,4 see page 5, paragraph 1-2	1,2,4-7, 12,23,25
A	EP 0 367 746 A (RICHARDSON VICKS INC.) 9 May 1990 see page 4, line 17-18; claims 1-3 see page 5, line 5-8; claims 10-12 see page 5, line 22-29	1-3,8, 12,13, 23,25,26

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 94 27576 A (DANBIOSYST UK) 8 December 1994 see page 6, paragraph 2-4; example 1 see page 7, paragraph 4; claims 1-3,5,7,10 see page 8, paragraph 4 see page 9, paragraph 4 - page 10, line 2 see page 10, line 25 - page 11, line 2 see page 16, line 11-13 see page 17, line 24-26	1-4,11, 12,21

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